CDC UPDATE
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NCHSTP National Center for HIV, STD & TB PREVENTION

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Questions and Answers on the Thailand Phase III Vaccine Study and CDC's Collaboration

Q1: Who is conducting the AIDSVAX Phase III trial?

The Bangkok Metropolitan Administration (BMA) is leading the 3-year collaborative research trial. BMA is conducting the trial in conjunction with VaxGen, the Mahidol University Faculty of Tropical Medicine in Bangkok, and the HIV/AIDS Collaboration (a longstanding research collaborative between the Thai Ministry of Public Health and the CDC).

Q2: Why is the AIDSVAX Phase III vaccine trial in Thailand being conducted?

The development of an effective HIV vaccine is a public health priority throughout the world. Because no one knows for sure which vaccine, or type of vaccine, will be most effective, multiple vaccines are being explored simultaneously. This particular trial is being conducted to address the urgent need for an HIV vaccine in Thailand and other developing nations. Because of the severe and escalating toll of HIV in Thailand, Thai government and public health officials have developed the Thai National Plan for HIV Vaccine Research. Through this plan, Thai officials are coordinating their efforts to help find an effective vaccine to slow the HIV epidemic in their country.

The VaxGen Phase III trial is part of that plan. VaxGen, Inc., a biomedical research company located in San Francisco, California, developed the candidate vaccine to be evaluated, AIDSVAX, and will fund most aspects of the study. VaxGen worked closely with Thai officials to ensure that AIDSVAX was designed to work against the subtypes of HIV most common in Thailand (i.e., subtypes B and E).

Q3: What is the trial designed to do?

The Phase III trial is designed to determine if AIDSVAX is effective in protecting against HIV infection and disease. While Phase I and II trials have already demonstrated that the vaccine is safe for use and is capable of inducing antibodies against HIV infection, it is not known if the level and type of antibodies produced will prevent HIV infection. This trial will answer that question. Large-scale human testing (called a Phase III trial) is the last and most important step in the evaluation process before a vaccine is considered for licensing.

Q4: How is the trial designed?

The trial is being conducted among uninfected injection drug users (IDUs) attending 17 drug treatment clinics in Bangkok. The design is a randomized, double-blind, placebo-controlled trial in which half of the 2,500 volunteers receive the AIDSVAX vaccine being evaluated and the

other half receive placebo injections that do not include the vaccine. Neither the researchers nor the participants know which participants are in each half of the trial. To guard against any of the participants relaxing their preventive behaviors, all volunteers receive extensive counseling on how to protect themselves against HIV infection, as well as explicit warnings that it is unknown whether or not this vaccine will protect them from infection.

Q5: Why is this particular vaccine being evaluated?

Thai officials chose to work with VaxGen to evaluate this vaccine because it has proven safe and effective in stimulating an immune response against HIV subtypes E and B, the subtypes most common in Thailand. If AIDSVAX proves to have a protective effect, it would therefore be effective against the subtypes causing the local Thai epidemic. AIDSVAX is also the first vaccine to receive approval for large-scale human testing (Phase III trials).

Q6: How does this vaccine work?

AIDSVAX uses a genetically engineered protein (gp120) from the surface of the human immunodeficiency virus. When injected into the body, it stimulates production of antibodies to attack any future invading HIV. Researchers hope the antibodies will prevent the virus from binding to, and infecting, healthy T-cells. AIDSVAX is a "bivalent" vaccine, meaning that it uses gp120 proteins from the surface of two different strains of HIV. The formulation of AIDSVAX being tested in Thailand uses HIV subtypes E and B, the subtypes most common in Thailand.

Q7: Why do only some of the participants receive the vaccine? Do the other participants get any benefit from the trial?

A placebo-controlled design (where some of the participants receive the vaccine being tested and some receive no vaccine) is currently the only scientifically sound way to determine if a vaccine works. In order to determine how effective the vaccine is, researchers will compare the rate of HIV infection in participants who receive the vaccine to the rate among those that receive the placebo injection. If people in the vaccine group have lower rates of infection than people with similar risk behaviors in the group that receives the placebo injection, then researchers will know the vaccine works. If the rates of infection are the same in both groups, researchers will know the vaccine does not work.

Everyone in the trial, regardless of the vaccine's effectiveness, is expected to benefit from participation in the trial. First, all IDUs participating in the trial are automatically enrolled in drug treatment and maintenance programs at the Thai clinics to help them stop using drugs and reduce their risk for HIV infection. Second, all volunteers receive the best available counseling on how to reduce their risk for HIV infection through behavior change. Individualized counseling sessions are based on CDC guidelines for the type of risk-reduction counseling that is most effective. Finally, all volunteers are encouraged to participate in group education sessions that focus on building peer support for reducing HIV risk.

Q8: In the Thailand AIDSVAX trial, one in two participants will receive the trial vaccine (the other will receive a placebo), yet in the U.S. AIDSVAX trial, two out of three participants will receive the trial vaccine (the other will receive a placebo). Why the difference?

The primary reason for the difference in vaccine to placebo ratio in the two studies is to account for the wider genetic diversity (range of HIV strains) in the United States, compared to Thailand.

In the U.S., the prevalent subtype B has been present since the mid-to-late 1970s and has over two decades to genetically diverge. By comparison, the Thai epidemic did not begin until 1988, and the subtype E viruses predominant there are not as diverse.

Many researchers believe genetic diversity may have an effect on vaccine protection, and that an HIV vaccine that is protective against some strains may not be effective against others. It is therefore important to ensure that each study will produce enough data to reliably analyze the vaccine's protective effect against the range of strains present in that nation. To statistically account for the wider genetic diversity in the U.S., it was necessary to include a greater proportion of vaccinated individuals in the U.S. study.

Q9: How do you expect to determine if the vaccine prevents infection if you are counseling everyone to protect themselves from exposure?

Health officials have an obligation to ensure that all participants benefit from proven prevention methods as we search for new ones. And while risk-reduction counseling has proven effective in reducing IDUs' risk for HIV infection, it has not proven effective in totally eliminating HIV risk. If behavior change programs were 100% effective, we would not need an HIV vaccine. Regardless of the best efforts at HIV prevention counseling, some individuals will continue to take risks. By comparing the rates of infection among those at risk in both groups, researchers will be able to determine if the vaccine helps protect these individuals from infection.

Q10: Do the participants know that some do not receive any vaccine?

Yes. Because of possible language and educational barriers, Thai health officials have worked with CDC, local clinic staff, and IDUs themselves to design an extensive process to ensure that volunteers understand what their participation in the trial means, exactly what they receive and do not receive as part of the trial, and that trial participation does not protect them from infection. Potentially eligible volunteers participate in an education session on the nature of the study (which includes a video) and then are given the opportunity to ask questions. Following this session, they complete a comprehension test, followed by discussion of the correct answers. After taking materials home to discuss the study with their family and peers, potential participants are asked to return to complete a second comprehension test. Those who are unable to pass the comprehension test are not enrolled. Those who do pass then undergo the informed consent process before being enrolled. All counseling sessions and materials are in the native language and have been locally evaluated for reading level and comprehension.

Q11: If participants become infected during the course of the trial, are they provided medical care?

Yes, the BMA has committed to providing medical care to any participants who become infected according to the *Bangkok Metropolitan Administration Guidelines for Clinical Care of HIV-Infected Patients (27 May 1998).* These guidelines state that HIV-infected persons will receive prophylaxis for tuberculosis and *Pneumocystis carinii* pneumonia (PCP), and that two antiretroviral drugs – AZT and ddI, ddC, or 3TC – will be administered to HIV-infected individuals when their CD4 counts drop below 500 or if the person develops an HIV-related disease. As part of the trial, participants are provided CD4 and viral load monitoring. CDC is working with BMA to ensure that local standards of care are implemented and that the Thai Ministry of Public Health and local physicians continue to review the standards as clinical management evolves.

Q12: Why not provide participants who become infected the same treatments available in the United States?

Thai government and health officials feel very strongly that treatment should follow the protocols they have established for their country. The triple drug therapies currently being used in the United States are not considered feasible for use in Thailand, not only because of cost constraints, but also because of issues related to the complexity of the regimen, the necessary follow-up and monitoring of patients, and tolerance to the therapies. Additionally, providing therapies not routinely available in Thailand to trial participants would be considered an unfair inducement to join the trial.

Q13: Why has there been skepticism about the potential effectiveness of AIDSVAX?

The AIDSVAX vaccine was developed over a period of a decade. The first version of the vaccine was based on only one strain of HIV. Because of the increasing genetic diversity of HIV across the globe, many believed it was important to add additional strains. VaxGen has since improved the vaccine, which is now based on these two strains of HIV. For use in Thailand for example, it was necessary to add an HIV strain from the subtype E virus, which is predominant in Thailand. The vaccine used in Thailand is composed of both subtype B (MN strain) and subtype E (A244 strain) antigens. For other areas of the world where the HIV subtypes may differ, the vaccine would have to be manipulated based on the strains common in those particular areas.

Additionally, no one knows for sure what type of immune response in vaccine recipients will be needed to prevent HIV infection. Some researchers believe that antibodies alone will be effective, but others believe that both antibodies and specialized immune cells (called killer T-cells) will be required to protect against infection. The VaxGen vaccine induces only an antibody response, while other vaccines under development combine this approach with a killer T-cell response. This and other studies ultimately will be required to determine whether either approach works.

Q14: Has this vaccine been studied in the United States? Why conduct the study in Thailand?

VaxGen is conducting a similar trial in the United States, but with a version of AIDSVAX designed to protect against the HIV strains common in North America. That study, which began in June 1998, will involve 5,000 volunteers at high risk for sexual HIV infection in 30-40 cities and will be completed by June 2001.

Thai health officials have decided to evaluate the AIDSVAX formula designed to work in Asia and the Pacific Rim as part of their efforts to find a vaccine that will be effective in their country. They are evaluating the vaccine among IDUs because HIV is now spreading rapidly among that population in Thailand. Among IDUs in Bangkok, 6% become infected each year, despite methadone treatment, education and counseling on HIV prevention, and easy access to sterile needles. A vaccine is urgently needed to slow this epidemic.

Q15: What is CDC's role in the trial?

For nearly a decade, CDC has worked closely with Thai public health officials to design and evaluate prevention efforts to help stop the Thai HIV epidemic. In 1990, CDC established a permanent field station in Thailand and a collaborative research program with the Thai Ministry

of Public Health – the HIV/AIDS Collaboration. Through this longstanding collaboration, CDC has worked closely with Thailand to address its evolving prevention needs.

Over the past several years, CDC has applied its experience in studying disease transmission and prevention to help the Thai government prepare to implement vaccine studies. Since 1995, this collaboration has involved a range of activities, including measuring the level of new (or incident) HIV infections in Thailand, determining the genetic characterization of incident HIV infections, identifying risk factors for infection, identifying a group of individuals who were willing to participate and could be followed over time to evaluate risk behaviors and infection, and working with the community to build the understanding and support necessary to implement vaccine studies.

In addition, in collaboration with the BMA, Faculty of Tropical Medicine of Mahidol University, and VaxGen, CDC has provided technical assistance in the development of the protocol, data forms, questionnaires, study procedures, and informational materials.

As the VaxGen study proceeds, CDC will continue to provide technical consultation as needed, laboratory testing and processing, and assistance in the analysis of study results. More importantly, perhaps, CDC will provide scientific support in the design and implementation of effective risk-reduction counseling for study volunteers and in the monitoring of behavioral risk factors. It is critical that participants in the study not abandon proven prevention methods (i.e., safer drug-related and sexual behaviors) as we search for new ones.

Q16: What ethics reviews were done (in the United States and Thailand) before beginning this trial?

To ensure an ethically sound study, all plans for the study, as well as consent procedures and educational materials, have been carefully reviewed and approved by multiple committees in Thailand, the United States, and internationally.

In Thailand, the trial has received an ethics review and approval from the Bangkok Metropolitan Administration, the Faculty of Tropical Medicine of Mahidol University, the Ethical and Scientific Review Committees of the Thailand Ministry of Public Health (MOPH), and the Thailand Food and Drug Administration. The Thailand MOPH also requested independent review and approval from UNAIDS. The UNAIDS review was conducted by the UNAIDS Vaccine Advisory Committee and a number of outside international experts on vaccine trials.

In the United States, the trial has received an ethics review and approval from the U.S. Food and Drug Administration and will soon receive additional approvals based on ethics reviews by the CDC Institutional Review Board (including representation by NIH) and the NIH Office for the Protection of Research Risks. Additionally, study plans have been presented to the Ethics Subcommittee of the CDC External Advisory Group.

Q17: Is CDC Involved in other vaccine trials?

Currently, the only other Phase III trial underway is the VaxGen study in the United States. CDC is planning to assist VaxGen with its U.S. study as well, but has not yet begun those efforts. CDC's role in that trial will be similar, and the agency will work to evaluate the impact of the trial on both participant and community attitudes and behaviors. Additionally, CDC will provide expertise in HIV surveillance in order to assess HIV subtypes and resistance. This information will be critical, not only for the communities currently involved, but also for the future

evaluation and implementation of vaccine strategies.

Q18: How does CDC's role complement that of NIH in HIV vaccine development?

CDC and NIH bring unique expertise and experience to the search for an HIV vaccine. In general, NIH has led the nation's basic research efforts to develop vaccines that may prevent HIV infection. This involves extensive cellular and laboratory research on the mechanisms of infection and the development of strategies to interfere with those mechanisms. NIH also is responsible for coordinating the simultaneous evaluation of multiple vaccine candidates.

To complement NIH's expertise, CDC has a long history in the field of vaccine evaluation, including evaluation of the measles vaccine, the hepatitis B vaccine, and the vaccine for *Haemophilus influenzae* type B disease. As the nation's lead prevention agency, CDC will be responsible for developing policies and procedures for effectively using an HIV vaccine, once a safe and effective vaccine is available. CDC has extensive experience in HIV prevention research and in working with states and communities to design and evaluate HIV prevention strategies. Until now, CDC's vaccine efforts have related primarily to working with communities and individuals to help researchers better understand attitudes and behaviors related to vaccines, including what factors influence people's willingness to participate in vaccine studies and use a vaccine and how vaccine studies may influence risk behaviors. Now, as large-scale evaluations of HIV vaccine candidates begin, CDC will play an increasingly important role in the design and evaluation of these studies and their impact on HIV transmission and related attitudes and behaviors.

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